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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/734,443	10/17/1996	BRUCE A. KEYT	A-63096/WHD	1390

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EXAMINER

SAOUD, CHRISTINE J

ART UNIT	PAPER NUMBER
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1647

36

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/734,443

Applicant(s)

KEYT et al.

Examiner

Christine Saoud

Art Unit

1647



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jul 23, 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18-35 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

Art Unit: ¹⁶⁴⁷~~1646~~

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 23 July 2002 has been entered.

Response to Amendment

2. Claims 1-14 and 16 have been canceled and claims 17-34 have been added as requested in the amendment of paper #35, filed 23 July 2002. Applicant should note that in paper #30, claim 17 was proposed to be added. According to 37 CFR 1.126, the original numbering of the claims must be preserved throughout the prosecution and when "claims are added, they must be numbered by the applicant consecutively beginning with the number next following the highest numbered claim previously presented (whether entered or not)". Therefore, the added claims have been renumbered and claims 18-35 are pending in the instant application.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Art Unit: 1646

4. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed 23 July 2002 have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 18-26 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for substitution with aspartic acid, does not reasonably provide enablement for any amino acid modification as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons of record in paper #26 and 28 as applied to claims 1-3 and 7-14. The rejection from paper #26 is repeated as follows.

The prior art of record identifies VEGF mutants which meet the structural limitations of the instant claims. The art teaches substitution of cysteine residues in VEGF with serine. The prior art specifically exemplifies the cysteine residues of the instant claims (see

Art Unit: 1646

Claffey and Potgens). Applicant has argued in the art rejection that Potgens teaches that the mutant VEGF proteins are not antagonistic. A review of Potgens confirms that these mutant proteins are not antagonistic (see page 32884, column 2, paragraph 3). However, this evidence also shows that the instant claims are not enabled for their full breadth. As demonstrated in Potgens and Claffey, these cysteine residues are necessary for disulfide bonding and dimerization of the VEGF protein. As stated by Potgens at page 32884, VEGF must dimerize in order to bind to its receptor, and receptor binding is a prerequisite for antagonism. Potgens demonstrates that mutation of the cysteine residues interferes with dimerization and therefore, receptor binding. Therefore, Potgens appears to teach away from mutating these cysteines in order to make an antagonist.

The instant specification discloses mutation of the cysteine residues (specifically at positions 51 and/or 60) result in an antagonistic molecule. This result is unexpected based on the teachings of Potgens. Because this result is unexpected, claims limited to this substitution are not anticipated or made obvious by the prior art. However, these results cannot serve as a basis for enablement of the broad claim, because evidence of Potgens demonstrates that not each and every amino acid substitution or amino acid modification will result in an antagonist. It is not clear which amino acid substitutions or amino acid modifications would provide for the desired biological activity. The specification only provides guidance for aspartic acid substitution and the art would suggest that it would be unpredictable to substitute other amino acids in light of the result with serine substitution. Therefore, the experimentation that would be required to practice

Art Unit: 1646

the full breadth of the claims would be undue because one would not have a reasonable expectation of making a substitution or modification, expect for the substitution of aspartic acid, and obtain a functional protein with the required biological activity.

One could argue that substitutions could be made and the resultant protein could be tested for biological activity. However, this is merely an invitation to experiment. Such a suggestion is found in Potgens (see page 32884, column 2, paragraph 3), however, this cannot serve as a basis for a rejection over the prior art and it therefore, cannot serve as a basis for allowance of the generic claim either.

Applicant repeats previously presented arguments stating that the substitutions could be evaluated by routine screening, that the specification provides direction and guidance by providing examples of methods used in creating and screening VEGF mutants, Applicants have demonstrated modification of specific cysteine residues which prevents disulfide bond formation. These arguments are still not persuasive for the reasons of record in paper #28. Briefly, Applicant's argument that the present disclosure, along with the general knowledge in the field, fully enables the skilled artisan to make and use the claimed invention without undue experimentation is not supported by any facts of record. The prior art of record identifies VEGF mutants which meet the structural limitations of the instant claims as well as teaching substitution of cysteine residues in VEGF with serine. The prior art specifically exemplifies the cysteine residues of the instant claims (see Claffey and Potgens). Applicant has previously argued that the mutant VEGF proteins of Potgens are not antagonistic, which is confirmed by Potgens at page

Art Unit: 1646

32884, column 2, paragraph 3. However, this evidence also shows that the instant claims are not enabled for their full breadth. The instant specification discloses mutation of the cysteine residues (specifically at positions 51 and/or 60) to aspartic acid result in an antagonistic molecule. This result is unexpected based on the teachings of Potgens. Because this result is unexpected, claims limited to this substitution are not anticipated or made obvious by the prior art. However, these results cannot serve as a basis for enablement of the broad claim, because evidence of Potgens demonstrates that not each and every amino acid substitution or amino acid modification will result in an antagonist. It is not clear which amino acid substitutions or amino acid modifications would provide for the desired biological activity. Furthermore, a single substitution is not predictive nor should it serve as a basis for the broad claim when the art specifically teaches another substitution encompassed by the claim which clearly is inoperative. The specification only provides guidance for aspartic acid substitution and the art would suggest that it would be unpredictable to substitute other amino acids in light of the result with serine substitution. Therefore, the experimentation that would be required to practice the full breadth of the claims would be undue because one would not have a reasonable expectation of making a substitution or modification, expect for the substitution of aspartic acid, and obtain a functional protein with the required biological activity.

Applicants argument that the disclosure provides direction and guidance because methods for creating and screening are provided is not persuasive. The instant rejection is based on the lack of guidance in the specification and the prior art for which substitutions should be made at

Art Unit: 1646

the cysteine residues to result in the claimed antagonistic molecules. A complete Wands analysis of the claimed invention was made, and it was concluded that the experimentation required to practice the invention would not be routine, but rather, undue in light of the lack of guidance, the lack of evidence, the state of the art at the time of the invention, the amount of experimentation required and the lack of predictability in the art.

Applicant asserts that the specification demonstrates that substitutions could be made, resulting in prevention of disulfide bond formation and the resultant protein could be tested for biological activity. However, this is merely an invitation to experiment because such a suggestion is already found in Potgens (see page 32884, column 2, paragraph 3), however, this cannot serve as a basis for a rejection over the prior art and it therefore, cannot serve as a basis for allowance of the generic claim either. Applicant again argues that working examples are provided, however, a single data point (substitution with aspartic acid) is not representative of the breadth of what is being claimed and further, a single species can rarely serve as a basis for a generic claim (see *In re Clarke*, 148 USPQ 665, (CCPA 1966)).

Conclusion

8. Claims 26 and 27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Art Unit: 1646

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Thursday from 8AM to 2PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556. If this number is out of service, please call the Group receptionist for an alternate number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTINE J. SAOUD
PRIMARY EXAMINER

Christine J. Saoud